

# Comparison of FDG-PET/CT for Cancer Detection in Populations With Different Risks of Underlying Malignancy

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**Abstract.** *Background/Aim:* Whole-body positron-emission tomography/computed tomography with the glucose analog 2-[<sup>18</sup>F]fluoro-2-deoxy-D-glucose (FDG-PET/CT) has been used to screen examinees for underlying malignancy in many countries. The aim of this study was to compare the potential value of FDG-PET/CT application in asymptomatic individuals with those with suspected malignancy. *Patients and Methods:* A total of 9,408 examinees underwent whole-body FDG-PET/CT at our hospital from July 2006 to August 2013. Three thousand and seven hundred asymptomatic individuals and 848 individuals with laboratory and clinical/radiological suspicion of malignancy who had undergone FDG-PET/CT for cancer screening were recruited. The final confirmation of cancer and outcomes were based on a pathological report and continuous follow-up. *Results:* Forty-five out of 3,700 asymptomatic individuals (1.2%) had proven malignancy, and 42 of them (93.3%) were found by FDG-PET/CT. Two hundred and twelve out of 848 with suspected malignancy (25%) had proven malignancy, and 196 of them (92.5%) were detected by FDG-PET/CT. Most of these cancers in asymptomatic individuals were clinically at an early stage. The discovery rate in asymptomatic individuals and those with suspected malignancy was 1.1% and 23.1%, respectively. The overall survival of patients with cancer diagnosed with PET/CT was higher than those with suspected malignancy (78.6% vs.

48.5%,  $p < 0.001$ ). Patients with a resectable lesion, early-stage disease, and lower maximal standardized uptake value had significantly better survival than those without. *Conclusion:* FDG-PET/CT is useful in the early diagnosis of cancer and thus might improve the survival rates of these patients. Considering the costs and risk of radiation exposure, it would be better used as a priority in patients with laboratory and clinical/radiologic suspicion of malignancy.

Cancer is a major public health problem worldwide and is the first or second leading cause of death in developed countries (1-3). Early detection of cancer is crucial for initiating treatment, prolonging survival, reducing mortality and the economic burden. To achieve early detection, various modalities for cancer screening have been developed, studied, and debated (3, 4). The National Cancer Institute in the US has estimated that 3% to 35% of premature deaths could be avoided through cancer screening (5). Like various tumor markers, conventional cancer screening is organ specific. In other words, conventional screening cannot detect cancer outside of the target organ nor determine disease severity. Four conventional cancer screenings including mammography, Papanicolaou smear, fecal occult blood and oral mucosa cytology are provided free to a selected population in Taiwan. Standard tests including physical examination, blood, urine and stool tests, serum tumor markers [cancer antigen-125 (CA-125), CA-153, carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP) and CA 19-9 for women, and prostate specific antigen (PSA), CEA, AFP and CA-199 for men], as well as chest film and abdominal sonography, are also performed every 2 to 3 years. Ideally, cancer screening should be a non-invasive and painless procedure that can reliably detect various types of cancer at a potentially curable stage regardless of location (3). Positron-emission tomography with the glucose analog 2-[<sup>18</sup>F]fluoro-2-deoxy-D-glucose (FDG-PET) has been increasingly recognized as a powerful tool with

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which to evaluate various malignant tumor types. FDG is an analog of glucose that is taken up and trapped in cells and is labeled with a positron-emitting isotope. FDG-PET is an imaging method based on the increased rate of glucose metabolism in malignant tumors that can be detected prior to anatomical changes. FDG-PET also provides improved differentiation of tumor malignancy and has high sensitivity for tumor detection. However, there is physiological FDG uptake in the brain, ocular muscles, nasopharynx, tonsils, salivary glands, intrinsic laryngeal muscles, heart, great vessels, breasts, liver, spleen, pancreas, stomach, intestines, kidneys, ureters, urinary bladder, genital organs, bone marrow and muscles. Additionally, several benign processes, particularly inflammation, also lead to higher uptake of FDG. The recognition of the physiological uptake of FDG and these benign processes is important in order to avoid the misinterpretation of PET. In a nationwide questionnaire survey of cancer screening in Japan, the cancer discovery rate of 1.4% associated with FDG-PET was much higher than the 0.1% rate for conventional cancer screening (3). Combined PET and computed tomography systems (PET/CT) have emerged as promising imaging modalities, gradually replacing PET and becoming more routinely applied clinically. With the ability of CT to provide anatomical mapping images and attenuation correction data, PET/CT can reduce the false-positive rate and improve the specificity compared with PET alone (3-5).

At the PET center of our hospital, some FDG-PET/CT scans were performed for cancer screening in a healthy population and cancer detection in some for those exhibiting a relatively higher incidence of cancer. We collected the FDG-PET/CT results of asymptomatic individuals and those with suspected malignancy (elevated tumor markers, clinical or radiological suspicion of malignancy) at our PET center. The aim of this study was to compare the potential value of FDG-PET/CT application in these two groups and further evaluate the cancer discovery rate and overall survival.

## Patients and Methods

**Participants.** We retrospectively collected data from examinees who underwent FDG-PET/CT scans at our hospital. A total of 9,408 examinees underwent whole-body FDG-PET/CT from July 2006 to August 2013. Four thousand five hundred and forty-eight cases without a history of cancer were included and were divided into two groups: asymptomatic individuals (group 1) and subjects with suspected malignancy (group 2). According to the study application forms, 3,700 cases were asymptomatic, 313 were referred due to a clinical suspicion of malignancy, 308 were referred due to radiological suspicion, and 227 were referred due to elevated tumor markers. Among the 3,700 asymptomatic individuals, 323, 1,097, 1,396, 677 and 207 cases were in the  $\leq 4$ th, 5th, 6th, 7th and  $\geq 8$ th decades of life, respectively. After the completion of the FDG-PET/CT examination, an experienced attending physician provided a detailed explanation of the scan results to allay the doubts of the

participants while providing information. A concluding report was provided to each examinee within 1 week. If any examinee was suspected of having cancer, they were provided with a clinic appointment and introduced to doctor to provide appropriate treatment. The final confirmation of cancer and outcomes were based on a pathological report and continuous follow-up. This study was approved by the Kaohsiung Veterans General Hospital Institutional Review Board (VGHS13-CT12-16). The need for written or verbal informed consent to participate in this study was waived by the hospital ethics committee because of the retrospective nature of the study.

**FDG PET/CT imaging.** Examinees fasted for at least 6 hours prior to whole-body FDG-PET/CT imaging. An intravenous catheter was placed for radiopharmaceutical administration, and the examinee's blood glucose level was measured prior to injecting the tracer. All the examinees exhibited a blood glucose level  $<150$  mg/dl at the time of injection. Each examinee received 370–555 MBq of  $^{18}\text{F}$ -FDG, according to their body weight (7.03 MBq/kg). After the tracer injection, the examinees rested for 1 hour on a comfortable bed in a dark room. Whole-body FDG-PET/CT imaging (Discovery ST-16; GE Healthcare, Milwaukee, WI, USA) was performed from the head to the upper thigh with the examinee in a supine position. A delayed image, with or without the use of diuretics, was obtained when necessary. CT scanning was performed prior to PET imaging. The following parameters were used: 0.6 s per rotation: 120 kV, 100 mA, and 3.75-mm-thick slices. After CT scanning, PET images of the same regions were acquired in the 2D mode, and 4 min of data were collected per bed position. Attenuation-corrected PET images were reconstructed using an ordered subset expectation maximization iterative reconstructed algorithm. The 3.75-mm thick transaxial CT images were reconstructed at 3.27-mm intervals for fusion with the PET images. PET, CT, and fused PET/CT images were generated on a Xeleris image display and processing platform (GE Healthcare) for review on a computer workstation.

**Image analysis.** The PET, CT, and fused PET/CT images were interpreted by two qualified nuclear medicine physicians who were allowed to manipulate the image contrast, image intensity, and 3D images on a computer screen. The final diagnoses were made by consensus. The physicians were not blinded to the medical history or outcomes at the times of image analysis. Prior imaging, especially prior contrast-enhanced CT scans, was available at the time of review to enable the fullest analysis. Both physicians reviewed the data independently before reaching a consensus. Any increase in the FDG uptake was compared with the corresponding anatomical findings on the CT image. For areas with abnormal FDG uptake, the physicians outlined the region of interest (ROI), which indicated the area with the greatest amount of uptake. The standardized uptake value (SUV), a marker of tumor glucose metabolism, was determined semi-automatically using the SUV tools available in the Xeleris software package as:  $\text{SUV} = \text{activity in the ROI (Bq/g)} / [\text{injected dose (Bq)} / \text{body weight (g)}]$ . The two-dimensional ROI was drawn around the tumor on each transaxial slice that contained tumor tissue. A single-pixel maximal SUV (SUVmax) was determined for each region, and the slice with the highest SUV was considered to be the SUVmax for the entire tumor.

**Statistical analysis.** The results were analyzed on a pathological basis, via imaging modalities, or with clinical follow-up evaluations.

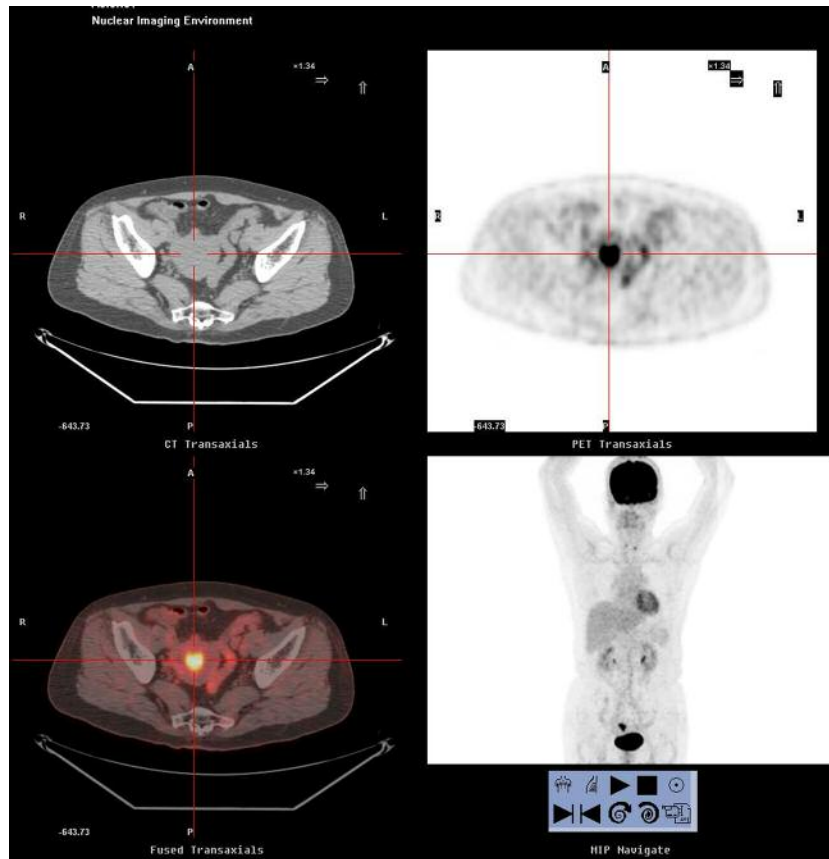


Figure 1. Positron emission tomography/computed tomography (PET/CT) in a 60-year-old asymptomatic post-menopausal woman with no indication of systemic disease. PET/CT demonstrated increased 2-[ $^{18}\text{F}$ ]fluoro-2-deoxy-D-glucose uptake in the central portion of the uterus (maximum standard uptake value: 10.3, cross cursor). Dilation and curettage were performed, and malignancy was demonstrated by pathological analysis. She underwent abdominal total hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic and para-aortic lymph node sampling, which showed moderately differentiated endometrioid adenocarcinoma, without lymph nodal metastasis. The pathological classification was stage I. She has been free of the disease for more than 10 years.

The discovery of cancer was defined as the detection of a malignant lesion within 12 months of the whole-body FDG-PET/CT scan. Chi-squared test was used to examine the differences between groups. Differences were considered to be significant at  $p < 0.05$ . The curve for cumulative survival from the time of FDG-PET/CT was derived from Kaplan–Meier method. All the calculations were performed using SPSS software, version 20.0 (SPSS, Chicago, IL, USA).

## Results

**Cancer detection.** Forty-five out of 3,700 (1.2%) examinees in group 1 had proven malignancy. Forty-two of them (93.3%) were found by FDG-PET/CT. The tumors of three patients, two with prostate cancer and one with urinary bladder cancer found within 1 year, were not detected by PET/CT. Two dual cancer cases were detected: one had lung cancer and cervical cancer, and the other had endometrial and ovary cancer. The distribution of these malignancies was

as follows: lung cancer in nine, colorectal cancer in nine, breast cancer in seven, thyroid cancer in four, nasopharyngeal cancer in three, prostate cancer in three, ovarian cancer in three, endometrial cancer in two (Figure 1), and lymphoma, brain cancer, renal cancer, urinary bladder cancer, cervix cancer, neuroendocrine tumor (NET) and hepatoma in one case each. The cancer detection rates according to the age distribution were 0.9% (3/323), 1.0% (11/1,097), 1.2% (16/1,396), 1.6% (11/677) and 1.9% (4/207) in the  $\leq 4$ th, 5th, 6th, 7th and  $\geq 8$ th decades of life, respectively. The stages of the malignant tumors according to the seventh edition of the American Joint Committee on Cancer (AJCC) Classification (6) were as follows: Stage 0 in four, I in 25, II in eight, III in seven, IV in two, and unclassified in one. For the three tumors not detected by PET/CT, there was one case each of stage I, II and III. Fifty-four patients with positive PET/CT had benign lesions. These

Table I. Proven cases of cancer detection in asymptomatic individuals (group 1) and individuals with suspected malignancy (group 2).

Cancer	Group 1			Group 2		
	PET/CT			PET/CT		
	Cases	+	-	Cases	+	-
Brain	1	1	0	0	0	0
Nasopharynx	3	3	0	3	3	0
Larynx				1	1	0
Thyroid	4	4	0	7	7	0
Lung	8	0	0	69	67	2
Breast	7	7	0	49	39	10
Colorectal	9	9	0	8	7	1
Ovary	2	2	0	7	7	0
Cervix				1	1	0
Kidney	1	1	0	1	1	0
Prostate	3	1	2	3	3	0
Liver	1	1	0	12	11	1
Stomach				5	4	1
Pancreas				18	18	0
Cholangiocarcinoma				6	6	0
Duodenum				3	3	0
Urinary bladder	1	0	1	1	1	0
Lymphoma	1	1	0	7	7	0
Multiple myeloma				1	0	1
Malignant thymoma				1	1	0
Mediastinal germ cell				1	1	0
Chondrosarcoma				1	1	0
Neuroendocrine	1	1	0	1	1	0
Endometrium	1	1	0			
MUO				3	3	0
Dual cancer	2	2	0	3	3	0
Total	45	42	3	212	196	16

MUO: Malignancy of unknown origin, PET/CT: positron-emission tomography/computed tomography.

included 22 patients with a benign tumor (nine brain, three uterine, two adrenal, two thymomas, one teratoma, one thyroid adenoma, one liver hemangioma, one splenic hemangioma, two lymphadenopathies), five with inflammatory disease (four tuberculoses and one non-necrotizing granulomatous inflammation) and 27 with pre-cancer (26 colorectal adenomas and one atypical ductal hyperplasia of the breast). Another two examinees had stone-induced hydronephrosis and marked hydrocephalus and received immediate manipulations.

Two hundred and twelve out of 848 (25%) examinees in group 2 had proven malignancy. One hundred and ninety-six of these malignancies (92.5%) were detected by FDG-PET/CT. Sixteen patients had cancer found within 1 year that were not detected by FDG-PET/CT. These were 10 breast, two lung, and one end of colon, one gastric, one hepatoma, and one multiple myeloma. The distribution of different

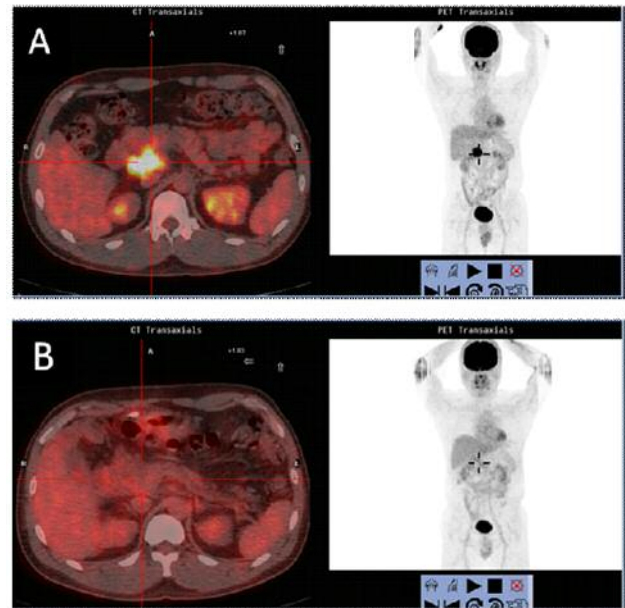


Figure 2. A 37-year-old man presented with jaundice and epigastric pain of 6 months' duration, and elevated serum cancer antigen 19-9 (CA 19-9) level of 836 U/ml (normal range: <37 U/ml). Abdominal sonography and computed tomography found a dilated bile duct, but biopsy via endoscopic retrograde cholangiopancreatography twice found no malignant cells. A: Positron-emission tomography/computed tomography with 2-[<sup>18</sup>F]fluoro-2-deoxy-D-glucose (FDG-PET/CT) showed a 'hot' area at the pancreatic head (maximum standard uptake value: 14.5, cross cursor). The pathological classification was stage III. B: He underwent palliative bypass due to an unresectable lesion, radiotherapy and chemotherapy, which revealed good response on the subsequent FDG-PET/CT, and the serum CA 19-9 level returned to normal. However, the tumor relapsed, and his disease progressed. The patient died 20 months after the first PET/CT.

malignancies in group 2 is listed in Table I. Three of them had dual cancer: one had lung cancer and melanoma, one had breast cancer and lymphoma, and one had thyroid cancer and lymphoma. The stages of malignant tumors according to AJCC were as follows: Stage 0 in four, I in 58, II in 33, III in 57, IV in 60, unclassified in three. For the 16 tumors not detected by PET/CT, the stages of malignancy were 0 in three, I in 10, III in one, IV in one, and unclassified in one. Thirty-four patients with positive PET/CT had benign lesions. These included nine patients with a benign tumor (one each of pituitary macroadenoma, choroid lesion, uterine mass, round pneumonia of lung, cavernous hemangioma of the lung, sclerosing hemangioma of the lung, bone marrow disease, teratoma, and mediastinal mass), 11 with inflammatory disease (five of tuberculosis, three of sarcoidosis, two lymphadenopathies, and one necrotizing lymphadenitis) and 14 with pre-cancerous lesions (12

Table II. Review summary of cancer screenings by positron-emission tomography (PET) or PET/computed tomography (CT) in asymptomatic individuals.

Author	Year	Examinees, n	Cancer, n	PET		Detection rate (%)	Modality	Country
				+	–			
Yasuda <i>et al.</i> (7)	2000	3,165	67	36	31	1.1	PET	Japan
Kao <i>et al.</i> (8)	2001	299	9	7	2	2.3	PET	Taiwan
Shen <i>et al.</i> (9)	2003	1,283	18	15	3	1.2	PET	Taiwan
Chen <i>et al.</i> (10)	2004	3,631	58	47	9	1.3	PET or PET/CT	Taiwan
Ide (11)	2006	9,357	296	141	155	1.5	PET	Japan*
Minamimoto <i>et al.</i> (12)	2007	43,996	500	395	105	0.9	PET	Japan*
Kojima <i>et al.</i> (13)	2007	4,881	51	36	15	0.7	PET	Japan
Terauchi <i>et al.</i> (14)	2008	2,911	157	28	129	1.0	PET	Japan
Nishizawa <i>et al.</i> (5)	2009	1,197	22	11	11	0.9	PET	Japan
Lee <i>et al.</i> (15)	2009	1,336	16	11	5	0.8	PET/CT	Republic of Korea
Shibata <i>et al.</i> (16)	2011	19,189	339	223	116	1.2	PET	Japan
Minamimoto <i>et al.</i> (17)	2013	155,456	1,912	1,491	421	1.0	PET or PET/CT	Japan*
Sengoku <i>et al.</i> (18)	2014	1,750	32	19	13	1.1	PET or PET/CT	Japan
This study		3,700	45	42	3	1.1	PET/CT	Taiwan

\*Nationwide survey.

colorectal adenomas, one atypical ductal hyperplasia of breast and one severe dysplasia of uterine cervix).

The discovery rate of FDG-PET/CT in group 1 was 1.1% (42/3700), which is comparable to that in the literature (Table II). In group 2, the rate of cancer detection was 23.1% (196/848). The detection of a clinically suspected but radiological equivocal lesion is particularly meaningful. A 37-year-old man presented with jaundice and epigastric pain of 6 months' duration, and elevated serum CA 19-9 of 836 U/ml (normal range: <37 U/ml). Abdominal sonography and CT found a dilated bile duct, but biopsy *via* endoscopic retrograde cholangiopancreatography twice found no malignant cells. FDG-PET/CT showed a hot area at the pancreatic head (SUV<sub>max</sub>: 14.5), and the pathological classification was stage III (Figure 2).

**Diagnostic value of FDG-PET/CT.** FDG-PET/CT was used to detect the cancer of 42 patients in group 1 and 196 patients in group 2. Fifty-four false-positive and 3 false-negative diagnoses in group 1, and 34 false-positive and 16 false-negative diagnoses in group 2 were noted. Accordingly, the sensitivity, specificity, true-positive rate (PPV), negative-predictive value (NPV) and accuracy of FDG-PET/CT were as follows: Overall: 92.6%, 97.9%, 73%, 99.5% and 97.6%, respectively; group 1: 93.3%, 98.5%, 43.8%, 99.9% and 98.5%, respectively; and in group 2: 92.5%, 94.7%, 85.2%, 97.4% and 94.1%, respectively. The PPV of FDG-PET/CT in group 2 was significantly better than that for group 1 (85.2% *vs.* 43.8%, respectively;  $p<0.001$ ). No significant difference in the sensitivity, specificity, NPV and accuracy between these two groups ( $p>0.05$ ) was noted (Table III).

**Overall survival.** Group 1 patients with cancer were found to be significantly younger than those in group 2 ( $55.5\pm 11.0$  *vs.*  $60.5\pm 13.8$ ,  $p=0.009$ , Table IV). The median tumor SUV<sub>max</sub> values for group 1 and 2 patients with cancer were 4.9 (range=0.8-23.9) and 7.4 (range=0.9-40.2), respectively ( $p=0.002$ ). The median follow-up times were 67 (range=6-106) months and 43 (range=0-103) months, respectively. All 45 (100%) cases in group 1 and 212 (100%) cases in group 2 had histologically proven malignancy. The number of those with early-stage ( $\leq$ stage II) cancer in group 1 was significantly higher than that in group 2 (35/45 *vs.* 94/212,  $p<0.001$ ). Of patients with cancer, two out of 45 (0.4%) in group 1 and 60 out of 212 (28.3%) in group 2 had distant metastases ( $p=0.001$ ). Surgical resections were performed in 86.7% (39/45) of the group 1 patients and 62.7% (133/212) of the group 2 patients ( $p=0.002$ ). The others were treated mainly using radiotherapy/chemotherapy.

After continuous follow-up, 10 out of the 45 (22.2%) patients with cancer in group 1 and 115 of the 212 (54.2%) in group 2 developed disease progression or recurrence. Finally, nine cases in group 1 and 110 in group 2 expired at the end of the study. The mean time from diagnosis to death in these patients was 49 months (range=12-103 months) for group 1 and 19.5 months (range=0-96 months) for group 2 ( $p=0.024$ ). The overall survival was higher in group 1 than in group 2 (80.0% *vs.* 48.1%,  $p<0.001$ ). For those diagnosed with cancer by PET/CT, nine cases in group 1 and 101 in group 2 had died by the end of the study. The overall survival was significantly higher in group 1 than that in group 2 [78.6% (33/42) *vs.* 48.5% (95/196),  $p<0.001$ , Figure 3A]. Twenty-seven out of 117 patients with early-stage malignant

Table III. Efficiency of positron-emission tomography (PET) or PET/computed tomography for cancer detection in asymptomatic individuals (group 1) and those with suspected malignancy (group 2).

Category (n)	TP	FP	TN	FN	Sen (%)	Spe (%)	PPV* (%)	NPV (%)	Acc (%)
Group 1 (n=3,700)	42	54	3,601	3	93.3	98.5	43.8	99.9	98.5
Group 2 (n=848)	196	34	602	16	92.5	94.7	85.2	97.4	94.1
Total (n=4,548)	238	88	4,203	19	92.6	97.9	73.0	99.5	97.6

Acc: Accuracy; FN: false-negative; FP: false-positive; NPV: negative predictive value; PPV: positive predictive value; Sen: sensitivity; Spe: specificity; TN: true negative; TP: true positive. \* $p < 0.001$ , group 1 vs. group 2.

Table IV. Outcomes of patients with cancer in asymptomatic individuals (group 1) and those with suspected malignancy (group 2).

	Group 1 (n=45)	Group 2 (n=212)	p-Value
Age, years	55.5±11.0	60.5±13.8	0.009
Gender, M/F, n	18/27	105/107	0.245
Median SUVmax (range)	4.9 (0.8-23.9)	7.4 (0.9-40.2)	0.002
Histology, n (%)	45 (100)	212 (100)	>0.99
Early-stage, n (%)	35 (77.8)	94 (44.3)	<0.001
Distant metastasis, n (%)	2 (0.4)	60 (28.3)	0.001
Surgical resection, n (%)	39 (86.7)	133 (62.7)	0.002
Progression or recurrence, n (%)	10 (22.2)	115 (54.2)	<0.001
Death, n (%)	9 (20)	110 (51.9)	<0.001
Time from PET/CT to death (range), months	49 (12-103)	19.5 (0-96)	0.024

PET/CT: Positron-emission tomography/computed tomography; SUV<sub>max</sub>: maximal standardized uptake value. \*Of those with malignancy.

lesions who had undergone surgical resections died compared with 92 out of 140 others. There was a significant difference in the overall survival between these two patient groups (76.9% vs. 34.3%,  $p < 0.001$ , Figure 3B).

## Discussion

Whole-body FDG-PET has been used for decades to screen underlying malignancies in asymptomatic individuals. Cancer screening focuses on early detection to reveal curable cancer that would be fatal if left untreated. FDG-PET has the potential to detect various cancer types at a potentially curable stage (3-4). In this study, we collected the data of examinees without a prior history of cancer, who had undergone FDG-PET/CT scans and revealed malignant tumors in 42 out of 3,700 (1.1%) asymptomatic individuals, with a PPV of 43.8%, and in 196 out of 848 (23.1%) with suspected malignancy, with a PPV of 85.2%, respectively. The discovery rate in our cases of asymptomatic individuals was similar to that previously reported (5, 7-18). Most of the reported studies in the literature have focused on cancer screening in 'asymptomatic' individuals. Therefore, no other report can be compared with our results on individuals with suspected malignancy. In fact, some examinees came to our

hospital for cancer detection due to incidental or sudden findings of abnormal physical or laboratory abnormalities. We found a significant difference in the PPV in these two groups (43.8% vs. 85.2%,  $p < 0.001$ ). Minamimoto *et al.* demonstrated increased cancer discovery rates of 0.4%, 0.8%, 1.1%, 1.5%, 2.1% and 2.6%, and PPVs of 16.5%, 22.9%, 24.1%, 27.4%, 33.1% and 40.9% in those in the 4th, 5th, 6th, 7th, 8th and ≥9th decades of life, respectively (17). Lee *et al.* reported that cancer detection rates were 1.0%, 0.9%, 1.5%, 1.2% and 0.9% in the ≤4th, 5th, 6th, 7th and ≥8th decades of life, respectively (10). In our study, the corresponding cancer detection rates were 0.9%, 1.0%, 1.2%, 1.6% and 1.9%, respectively. The PPV in prior articles ranged from 3.3% to 70% (8, 9, 17, 19) in different populations of healthy asymptomatic participants, and 79% to 100% in patients with various known or suspected cancer (20-25). The discovery rate of cancer and PPV in our study supports the interpretation that the cancer discovery rate and PPV should be considered in the context of disease prevalence (10, 17, 26).

Inherent false-positive results for cancer screening exist, although patients can ultimately benefit from these findings. Fifty-four out of 3,700 cases in group 1 (1.46%) and 34 out of 828 in group 2 (4.1%) that were considered clinically

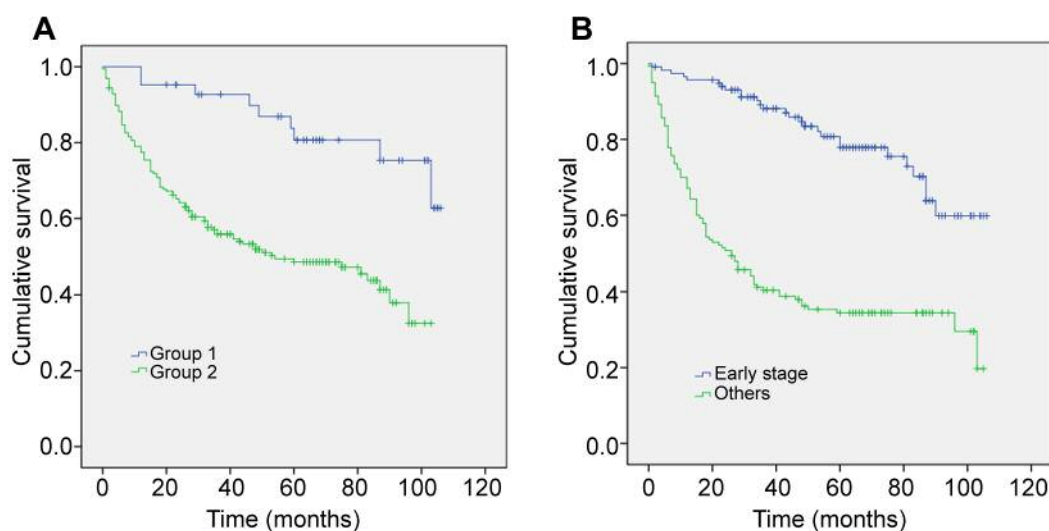


Figure 3. Cumulative survival curve of patients diagnosed with cancer by PET/CT in asymptomatic individuals (group 1) and with suspected malignancy (group 2) (A), and according to surgical resection stage tumor lesions (B).

important and required surgical intervention were histologically benign. Thirty-one (35.2%) were benign tumors, 16 (18.2%) were regarded as inflammatory disease, and the remaining 41 (46.6%) were pre-cancerous lesions. In the present study, false-positives also led to the surgical resection of significant tumors. The early detection of these diseases might lead to more effective treatment options and could improve patient survival. Furthermore, some significant infectious/inflammatory diseases were detected (27) and appropriately treated or referred for follow-up. In addition to those histologically proven cases, two examinees with stone-induced hydronephrosis and marked hydrocephalus on PET/CT went on to receive immediate manipulations.

Three out of 45 cases with cancer in group 1 (6.7%) and 16 out of 212 in group 2 (7.5%) were not detected by FDG-PET/CT. These were 10 breast, two lung, two prostate, and one each of urinary bladder, colon and gastric cancer, one hepatoma, and one multiple myeloma. The possible causes for false-negative FDG-PET were as follows: (i) Cancer with hypometabolic features or low accumulation of FDG; (ii) cancer with low cell density; (iii) cancer with high background activity (*e.g.* urinary tract); (iv) and small cancerous lesions (4, 10, 11). However, most of the cancer cases in this study were found at a clinically early stage: Stage 0 in three (all breast), I in 11 (seven breast, two lung, and one each of prostate and hepatoma), II in one (urinary bladder), III in two (one each of prostate and colon), IV in one (gastric), and unclassified in one (multiple myeloma).

Surgery is potentially curative for patients with limited sites of malignant disease, particularly those in the early stage (28-31). FDG-PET/CT is helpful in the selection of

patients who might derive significant survival benefits from optimal surgical strategies. The earlier recognition of resectable lesions hopefully will provide more effective treatment options and improve patient survival rates. In this study, surgical resections were performed in 86.7% (39/45) of patients in group 1 and 62.7% (133/212) in group 2 ( $p=0.002$ ). The number of early-stage ( $\leq$ stage 2) cancer in group 1 was significantly higher than that in group 2 [77.8% (35/45) vs. 44.3% (94/212),  $p<0.001$ ]. Furthermore, the median tumor SUVmax was lower in group 1 than in group 2 patients with cancer ( $p=0.002$ ). Pretreatment FDG-PET SUV was found to be a prognostic factor for outcome in many types of cancer (32-35).

In a health promotion proposal project supported by our Institution, hospital employees between 55 and 65 years old were provided the opportunity to undergo free whole-body FDG-PET/CT (26). This selected population exhibits a relatively higher incidence of cancer and is in the last decade before retirement according to the regulations of our government. The cancer discovery rate was 3.3% (3/92) with a PPV of 50% (3/6). The offer of whole-body FDG-PET for cancer screening was welcomed with enthusiasm by most hospital employees. Most of the participants (77/81, 95.1%) reported no sense of worry, anxiety, depression or psychological distress after the PET/CT examination. We believe that an immediate and detailed interpretation of the PET/CT results dispelled the doubts and fears of participants and encouraged participants to accept the scan results.

Whole-body FDG-PET/CT is expensive and carries with it risk from radiation exposure, and is not yet suitable for general use for cancer screening. Moreover, additional



examinations because of false-positive PET findings are not without risks. FDG-PET is commonly used for staging and restaging of many solid tumors. However, not all tumors take up high levels of FDG, which may cause challenges in scan interpretation. FDG uptake correlates with glycolysis levels and is generally much higher than that of normal tissues in many common malignancies including lung, breast, and colon cancer. Other tumor subtypes may have low-level uptake, including renal cell cancer, mucinous tumors, hepatocellular carcinoma, prostate cancer, low-grade lymphomas and low-grade adenocarcinoma spectrum lesions in the lungs (36-41). It is important to clarify the value of whole-body PET/CT for health screening including the issues of cost-effectiveness and the impact on cancer mortality (4, 42). A recent article suggested that FDG PET/CT scan can be performed as a first-line tool in the initial diagnosis of the patients with cancer of unknown origin and to add radiodiagnostic imaging in selective cases. If the first-line examination of a patient with cancer of unknown origin has already been performed by conventional imaging methods and the result was negative or inconclusive, FDG PET/CT can be considered to avoid further unnecessary imaging procedures (25). In this study, FDG-PET/CT had a high discovery rate in those with suspected malignancy, and a lower rate of false-positives and higher PPV than those in the asymptomatic individuals. PET/CT detection in selected individuals with suspected malignancy may be more valuable.

Our study had some limitations. Firstly, it was retrospective, and FDG-PET/CT was applied to a specific cohort of examinees who asked for a health check-up. Therefore, this might have resulted in some bias. Secondly, we actually limited whole-body imaging from the head to the upper thigh in most of the examinees because cancer below the thigh is rare in adults. Limited whole-body PET/CT has advantages over true whole-body PET/CT, primarily reducing the scanning time and radiation exposure (43-44). Finally, the total number of participants in this study was small. Additional studies with a prospective trial design investigating a specific cohort of patients would be valuable.

## Conclusion

FDG-PET/CT is useful in the early diagnosis of cancer and thus might improve the survival rates of these patients. In this study, FDG-PET/CT had high overall sensitivity and specificity for detecting cancer in different patient groups, and a higher discovery rate and PPV in those with suspected malignancy than in the asymptomatic individuals. The rate of detection of cancer in 1.2% in asymptomatic individuals is likely too low to justify population-wide screening with PET/CT. The only advantage of screening in asymptomatic individuals is that cancer can be detected at an earlier stage

with better prognosis. The utility of whole-body PET/CT for the surveillance of selected groups of patients who have a high risk for cancer would be more beneficial. In those suspected of having malignancy, the proportion of cancers was much greater, the stage was higher, and the incidence of distant metastasis was greater than in asymptomatic individuals. Therefore, FDG-PET/CT would be better used as a priority in individuals with laboratory and clinical/radiological suspicion of malignancy.

## Conflicts of Interest

The Authors declare no conflicts of interest in association with this study.

## Author's Contributions

N-J.P. designed the study. H-P.C., W-S.L., W-S.L., C.H., Y-L.C. collected data. C.H., Y-L.C analyzed the data. H-P.C., N-J.P. wrote the article. All Authors declare they significantly participated in creation of the study. All Authors approved the final article.

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